## REMARKS

Claims 1-43 are pending in this application with claims 1-18 and 22-38 currently being withdrawn from examination. As a result, claims 19-21 and new claims 39-42 are pending for examination with claim 19 being the sole independent claim. New claims 39-42 depend from claim 19, Applicant believes that new claims 39-42 also correspond to elected Group II, Species 1, Subspecies A. No new matter has been added.

### Rejections Under 35 U.S.C. § 103

*Medlen in view of Bell and MacPhee*

Claims 19-21 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Medlen (WO 85/00511) in view of Bell (6,153,292) and MacPhee (6,117,425). To support these rejections, the Examiner states that Medlen, Bell, and MacPhee may be combined and that MacPhee discloses a method using a composition including platelets to treat an intra-articular injury in a subject as claimed in claim 19. Applicants respectfully traverse these rejections as follows.

The October 17, 2003, telephone conference is made of record. Applicants gratefully acknowledge the courtesies extended to Applicants' attorney, Ms. Carole A. Boelitz, during the telephone interview. The substance of the discussions during the interview are incorporated into the following remarks.

As noted in Applicants' prior response, the Examiner's combination of references, even if combinable, do not teach or suggest the features of claim 19 including a composition comprising platelets. To show the addition of platelets to tissue repair implants, the Examiner specifically points to column 12, lines 13-18 and column 23, lines 32-40 of MacPhee. Upon review of these specific sections, as well as MacPhee as a whole, Applicants are unable to find any reference of the addition of *platelets* to any type of tissue sealant. Rather, MacPhee is directed to adding an effective amount of a platelet-derived extract such as platelet-derived growth factor or platelet-derived wound healing factor.

During the telephone interview, the Examiner suggested the equivalence of platelets and platelet derived wound healing factor as taught by MacPhee (column 23, lines 32-40). Applicants respectfully disagreed with this assertion. More particularly, platelets are cell fragments having a complex composition and function *in vivo*. To accomplish multiple

functions, platelets include many different growth factors and clotting factors, which may be separated from the main cell fragment of the platelet. After extracting the factor from the platelet, MacPhee specifically discloses that "the platelets are removed and an effective concentration of the remaining extract is added to a [tissue sealant]." (MacPhee, column 23, lines 38-40). In this manner, as noted in the telephone interview, MacPhee teaches away from including platelets in a repair composition since MacPhee discloses removing the platelets after the platelet derived factor is extracted. Thus, it is apparent that even if combined, Medlen in view of Bell and MacPhee does not disclose or suggest the features of claim 19 including contacting the ends of a ruptured tissue from the subject with a composition comprising soluble type 1 collagen, a platelet, and at least one of an extracellular protein and a neutralizing agent. Although no agreement was reached during the telephone interview, the Examiner agreed to review Applicants' comments and obtain input from the biotechnology examination group.

The Examiner also suggests the desirability of modifying or combining the invention of Medlen with both Bell and MacPhee. As noted in Applicants' prior response, however, MacPhee teaches away from the Examiner's proposed combination. The M.P.E.P. § 2145 states: "It is improper to combine references where the references teach away from their combination." Here, MacPhee teaches away from a combination with both Medlen and Bell. specifically, MacPhee notes that the tissue sealants disclosed should only contain proteins of human origin noting that the risks of allergic reactions, and bovine spongiform encephalopathy are not insignificant concerns. (MacPhee, Col. 4, lines 51-67; col. 13, lines 17-26). In contrast, the collagen implant of Medlen utilizes bovine skin collagen and Bell suggests that its source of biopolymers includes mammals such as pigs, sheep, and cows. Thus, MacPhee teaches away from the combination suggested by the Examiner.

It appears that the Examiner misunderstood Applicants' position since the Office Action indicates that "The fact that each of the references suggest *possible* sources of the elements in the composition that are different is irrelevant since the claims do not recite what the source of each of the elements are taken from." However, Applicants remarks regarding the source of the collagen are directed toward the non-combinability of the cited references and not to the specific features of claim 19 itself. Thus, since MacPhee suggests that non-human components such as collagen or protein should not be used, those skilled in the art would have no motivation to

combine or modify the teachings of Medlen or Bell in view of MacPhee. Accordingly, the rejection is unsupported by the art and should be withdrawn.

Moreover, Applicants disagree with the Examiner that these references can or should be combined. Initially, the implant disclosed in Medlen is attached to the ruptured ends of a ligament *in vivo*, whereas the ligament repair disclosed in Bell is conducted *in vitro*. There is no teaching or suggestion in either Bell or Medlen to suggest that the *in vitro* method or implant components of Bell may be combined with or modified for *in vivo* repair of ligament tissue as in Medlen.

Furthermore, the Examiner has not provided a motivation to combine Medlen with both Bell and MacPhee. Regardless of whether it may be possible to modify or combine Medlen in view of Bell and/or MacPhee, a motivation to combine or modify requires a teaching that such combination is clear and particular and desirable. In the Office Action, the Examiner indicates that the motivation to combine comes from the references as a whole since "the resulting composition is more like the tissue in which it is [to] be used for by adding the platelet, protein and neutralizing agent as taught in MacPhee and Bell respectively into the composition it provides the ability of the body of the subject to recognize it as being non-foreign." This is a non-specific, hindsight rationale clearly based on Applicants' own disclosure, and is entirely inadequate under the law. In fact, the *Examiner's* stated motivation *teaches away* from using either Medlen or Bell, since both of those references disclose using non-human collagen sources which decrease the stated motivation of providing "the ability of the body of the subject to recognize [the repair composition] as being non-foreign." Accordingly, Applicants respectfully suggest that the combination of references is improper and that the rejection of claim 19 in view of Medlen, Bell, and MacPhee be withdrawn.

For at least the foregoing reasons, Applicants maintain that independent claim 19 is patentable over Medlen in view of Bell and MacPhee, either alone or in combination. Dependent claims 20-21 depend from independent claim 19, and for at least the reasons set forth above, these claims are patentable over Medlen in view of Bell and MacPhee. Accordingly, withdrawal of this rejection is respectfully requested.

*Li in view of MacPhee*

The Office Action also rejected claims 19 and 20 under 35 U.S.C. § 103(a) as being unpatentable over Li (WO 93/21857) in view of MacPhee. Applicants respectfully traverse the rejection as follows.

Even if combined, the cited references of Li and MacPhee, either alone or in combination, do not teach or suggest the features of claim 19. More particularly, as noted above and in the telephone conference, MacPhee does not disclose or suggest a composition comprising a platelet. Li does not cure this deficiency, as noted by the Examiner in the Office Action. Moreover, Li does not teach or suggest contacting the ends of a ruptured tissue from the subject with a composition. The Examiner suggests that Li inherently discloses contacting the ends of ruptured tissue since Li is directed to ligament repair in intra-articular joints. However, Li is not directed to ligament *repair*, but rather, is directed to a *total replacement* ligament formed from collagen. Thus, the Li reference does not teach or suggest contacting the ends of ruptured tissues as recited in claim 19. Rather, Li completely replaces ruptured ligament tissue, i.e., attaches the implanted collagen braid from bone to bone and not from ruptured tissue to bone or to ruptured tissue. Thus, Li in view of MacPhee does not teach or suggest the features as recited in claim 19, and accordingly, Applicants respectfully suggest that the rejection should be withdrawn.

For at least the foregoing reasons, Applicants maintain that independent claim 19 is patentable over Li in view of MacPhee, either alone or in combination. Dependent claim 20 depends from independent claim 19, and for at least the reasons set forth above, is also patentable over Li in view of MacPhee. Accordingly, withdrawal of this rejection is respectfully requested.

## CONCLUSION

In view of the foregoing amendments and remarks, this application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this amendment, that the application is not in condition for allowance, the Examiner is requested to call the Applicants' attorney at the telephone number listed below.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicants hereby request any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,

*Martha M. Murray, M.D., et al., Applicants*

By: _____

Carole A. Boelitz, Reg. No. 48,958
Helen C. Lockhart, Ph.D., Reg. No. 39,248
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2211
Telephone: (617) 720-3500

Docket No.: B00801.70258
Date: November 14, 2003
**x11/17/03**